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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/346,470	07/01/1999	RONALD JOHNSTON HILL	53-99	2471

23713 7590 09/15/2006

GREENLEE WINNER AND SULLIVAN P C
4875 PEARL EAST CIRCLE
SUITE 200
BOULDER, CO 80301

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/346,470	HILL ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-85 and 88-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-81 and 88-95* is/are rejected.

7)☒ Claim(s) *82-84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/06, 8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicant's response of 10 July 2006 to the Non-Final Office Action of 9 January 2006 has been received and entered.

Claims 79-85 and 88-95 are pending in this application. Amendment to Claim 90 received on 10 July 2006 has been entered. Receipt of Exhibits A-D is acknowledged and these exhibits have been entered into the record. Applicants' arguments filed on 10 July 2006 will be responded to herein. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Objections Withdrawn

The objection to Claim 90 is withdrawn in view of Applicants' amendment to the claim to correct a typographical error.

Rejections Maintained

35 U.S.C. § 112, Second Paragraph

The rejection of Claims 79-81, 85 and 88-95 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record and for reasons outlined below.

Applicants traverse this rejection (page 5, 4th paragraph of response of 10 July 2006, bridging page 6, 1st paragraph). The reasons for traversal are that: (a) "use of 'consisting essentially of' is well understood in patent drafting to mean there cannot be

additional material that materially affect the basic and novel characteristic of the claimed invention"; (b) the specification defines "substantially identical" in the specification at page 23, lines 19-22.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The transitional phrase "consisting essentially of" is typically used and defined in the context of compositions of matter (See MPEP 2111.03). However, the term is unclear as utilized within the context of claims of the instant invention; the claims of the instant invention are drawn to a nucleic acid sequence, which is a compound and not a composition of matter. Additionally, the specification (page 23, lines 19-22) teaches that substantially identical is defined to include any sequence which is at least about 95% identical..... The use of "include" and "at least about" in the definition provided in the specification renders the term "substantially identical" indefinite.

35 U.S.C. § 112, First Paragraph:

The rejection of claims 79-81, 85 and 88-95 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is maintained for reasons of record and for reasons outlined below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants traverse this rejection (page 6, 4th paragraph of response of 10 July 2006, bridging page 6, 4th paragraph bridging page 7). The reasons for the traversal are that: (a) claims include functional limitations and the structure is limited in terms of substantially identical to or consisting essentially of a recited sequence; (b) the previous examiner indicated, in an informal telephone interview that examples of ecdysone receptors of at least 60% sequence identity to SEQ ID NO:10 would overcome the rejection; (c) applicants provide result of sequence comparisons in Exhibit A and B

indicating ecdysone receptors from diverse species of insects which are 72.9%, 73.4%, and 71.6% sequence identity to the exemplified SEQ ID NO:10.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

As discussed above, the terms "consisting essentially of" and "substantially identical" are vague and indefinite within the context of the recited claims. Therefore, the structural limitations of the claimed isolated nucleic acids cannot be determined. However, the specification does provide adequate support for sequences that are 95% identical to the exemplary sequences. (**Note to Lori: is this ok, since they do have a definition of substantially identical to include 95%)** Where in the spec? If it says it includes 95%, then they do have bases for 95% as a limit in a claim.

Applicants assert that in an informal telephone interview, the previous Examiner indicated that examples of ecdysone receptors of at least 60% sequence identity to SEQ ID NO:10 would overcome the rejection. However, the contents of this interview were not made of record, and therefore applicants' statements cannot be considered. The only interview made of record took place on 27 June 2002. The Examiner's notations indicate that a discussion of rejection under 102 and 112, first and second paragraph took place, but there is no written record of the decisions reached at this interview.

Exhibits A and B provide references indicating a 72.9% and 73.4% identity between the amino acid sequence (SEQ ID NO:10) of the instant invention and the amino acid sequences of the ecdysone receptor of *N. virdula* and a 71.6% amino acid identity between the amino acid sequence of the instant invention and the amino acid sequence of the edysone receptor of *B. tabacai*. However, neither Exhibits A and B, nor the specification provide alignment data to indicate which portions of the molecules need to be conserved and which may be altered and not result in a loss of edysone binding function. Thus, the specification and submitted exhibits A and B do not provide adequate guidance as to the nature of active derivatives that may be constructed, but are merely invitations to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional

Guidance must be in the spec.; not art submitted after the fact.

configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The ability of one skilled in the art to carry out site-directed mutagenesis, and test the resulting muteins for ecdysone-binding activity is not in question. However, to determine which amino acid substitutions may be made in expressed sequences of ecdysone receptor (either at ecdysone binding sites, or at surrounding residues) and still result in a protein retaining the required functional activity of an ecdysone receptor protein, i.e. ecdysone binding activity, would require undue experimentation.

The rejection of claims 79-81, 85 and 88-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record and for reasons outlined below. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse this rejection (page 8, 2nd and 3rd paragraph of response of 10 July 2006). The reason for the traversal is that techniques to determine ecdysone binding are well known in the art and that the claims are adequately enabled when the Specification is taken together with the knowledge of the art.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Applicants' reasons for traversal are directed to rejection based on scope of enablement of the claims. The traversal of the enablement rejection has been responded to above. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

The rejection of Claims 93 and 94 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising

an expression vector, is maintained for reasons of record and for reasons outlined below.

Applicants traverse the rejection (page 8, last paragraph of response of 10 July 2006 bridging page 9, 1st-4th paragraphs) on the grounds that: (a) the preponderance of host cells into which an expression vector carrying a coding sequence of the polypeptide of the instant invention operably linked to transcription regulatory sequence is introduced will exhibit expression of the particular coding sequence; and (b) the level of skill in the relevant art is very high and there is more than twenty years of experience in gene expression on which to draw.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. There is no question that vectors encoding the polypeptides of the instant invention can be introduced into isolated host cells or cells in culture, resulting in expression of the particular coding sequence. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells for this purpose. Undue experimentation would not be required of the skilled artisan to make and use the claimed host cells in this context. However, the specification also contemplates transgenic organisms (page 10, lines 15-16 and page 28, lines 22-30), and gene therapy in a variety of organisms, including humans (page 34, lines 3-10). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. Additionally, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Although gene therapy experiments have been carried out for twenty years, relevant

literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (2001. Phillips, A., J Pharm Pharmacology 53: 1169-1174, abstract, cited in previous office action). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism, particularly a human, to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Applicants have submitted a paper by No et al. (Exhibit C) which describes transgenic mice in which there is ecdysone-inducible gene expression in transgenic mice. The teachings of No et al are directed to making transgenic animals expressing the ecdysone receptor of *D. melanogaster.* The specification teaches that there is limited homology between the *D. melanogaster* steroid receptor-encoding gene sequences and the steroid receptor-encoding sequences derived from other insects (page 3, lines 16-19). Therefore, the successful production of transgenic mice by No et al. is not predictive of success in producing a transgenic animal with the incorporated claimed gene and demonstrating expression of the encoded peptide. Furthermore, No et al teach that a number of modifications must be made in the EcR to maximize the sensitivity of the ecdysone-inducible system; the reporter vector was also modified to boost transcriptional activity (page 3349, 1st column, 1st paragraph). The specification does not provide direction or working examples that would enable the skilled artisan to produce transgenic organisms expressing the protein of the claimed invention.

Applicants have submitted, as Exhibit D, a paper by Bender et al. which teaches three isoforms of the ecdysone receptor from *D. melanogaster.* The relevance of Exhibit D to the claims of the instant invention is unclear. Bender et al. characterize isoforms of the ecdysone receptor; however, these all contain the same DNA and ligand binding domains, and thus would not provide guidance as to which amino acids must be conserved to insure ecdysone binding. Furthermore, these isoforms are of proteins from *D. melanogaster;* the specification teaches that there is limited homology between

the *D. melanogaster* steroid receptor-encoding gene sequences and the steroid receptor-encoding sequences derived form other insects (page 3, lines 16-19).

Please note that the rejection of claims 93 and 94 could be overcome by amending the claims to recite, for example, "An isolated host cell..." because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture.

Objections

Claim(s) 82-84 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions:

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS